"FORMULATION DEVELOPMENT AND EVALUATION OF PRONIOSOMAL DRUG DELIVERY SYSTEM"

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Submitted

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1. Abstract of proposed work plan/ problem:

Nowaday's recent advances in the understanding of pharmacokinetic & pharmacodynamic behaviour of drug have offer a more rational approach to the development of optimal drug delivery system. Now it's appreciable that future success in drug delivery research will largely be result of multidisplinary efforts. If any therapeutic agent that can be the more efficacious and safe using and improved drug delivery system represent both lucrative marketing opportunities for pharmaceutical company and advancement in the treatment of diseases of mindkind. An ideally design drug delivery system delivers a specified amount of drug to target particular site at an appropriate time and rate as dictated or desired by the etiological and physiological needs of the body. Conventional Pharmaceutical Dosage forms are incapable of controlling the rate of drug delivery to target site. As a result the distribution of drug in nontarget tissue and body fluids necessitate therapeutic doses that could far exceed the amount required in target cells, the higher doses often lead to serious adverse during treatment thus, the novel drug delivery systems (NDDS) are carriers which maintain the drug concentration in therapeutic range for longer period of time and also, in addition, may deliver the content to the site of action if so desired as per requirements.

2. Introduction:

Cancer is a critical disease occurring due to progressive accumulation of epigenetic and genetic changes, leading to worldwide death. It is a category of disease characterized by uncontrolled,rapid abnormal growth of cells. The major disadvantage associated with anticancer drugs is their lack of selectivity for tumour tissue, resulting in several toxic effects leading to low cure rates. Methods available currently for cancer diagnosis and treatment are expensive and can be very harmful to the body. Presently, radiation therapy, chemotherapy, or surgery all of which can be successful are the most common cancer treatment methods based on, but have significant demerits. Though modern nanotechnology offers a possibility of materials that selectively bind to particular types of cancer cells, sensitizing them to light without affecting surrounding healthy tissues by selective targeting to tumour tissue is still a major worry. Cancer being a leading cause of death worldwide in 2022 is estimated to those 19.3 million new cases of cancer has occurred and an estimated 10 million people died from cancer.

Challenges in cancer chemotherapy:

Different routes of administration are frequently used in cancer therapies, particularly oral and intravenous administration. Most of the time, the therapeutic modality used dictates the choice of the administration route. Hence, oral delivery is the gold standard for some molecules. Cancerv treatment facing challenges like, some API'shave shown poor solubility with limited bioavailability. Hence are required chemical modification or formulation development. These active molecules may also exhibit adverse effects in normal tissues, which would limit their efficasy due to low therapeutic index. Consedering all these challenges, there is an increasing demand for effective and, ideally strategies in drug delivery system to ensure the delivery of the right drug, at the right location, over a right period of time while minimising side effects on healthy cells.

NOVEL DRUG DELIVERY:

Vesicular drug delivery system:

Vesicular drug delivery reduces the cost of therapy by improved bioavailability of medication. Especially in case of poorly soluble drugs. They can incorporate both hydrophilic and lipophilic drugs. Vesicular drug delivery systems delay drug elimination of rapidly metabolizable drugs, and function as sustained release systems. This system solves the problems of drug insolubility, instability, and rapid degradation. consequently number of vesicular delivery systems such as liposomes, niosomes, proniosomes, pharmacosomesetc. were developed.

Types of vesicular drug delivery systems:

- Liposomes
- Virosomes
- Niosomes
- Proniosomes
- Transferosomes
- Proteasomes
- Sphingosomes
- Archaesome
- Ethosomes.

Proniosomes:.

Proniosomes, being dry, free flowing products, minimizes stability problems during storage and sterilization and it has additional advantages of ease of transfer, distribution, measuring and storage which makes them a pronouncing versatile delivery system. Proniosomes are a dry, free-flowing, granular product which, upon addition of water, disperses or dissolves to form a multilamellar niosomal suspension, suitable for administration by oral or other routes. As proniosomes are having advantages over liposome as well as niosomes, by minimizing problems of physical and chemical stability during storage and sterilization, and it have additional merits of transfer, distribution, show high entrapment efficiency, capable of

releasing these drugs for the extended period of time. Hence the present study is focusing on the formulation and evaluation of proniosomes as drug delivery system for anticancer drug.

Table: Diff. bet. Liposomal, Niosomal &Proniosomal drug delivery

Sr. No.	Liposomes	Niosomes	Proniosomes
1	Leakage of encapsulated drug	Leakage of encapsulated drug	**Less Leakage of encapsulated drug**
2	Fusion	Fusion	**Less fusion**
3	Aggregation	Aggregation	**Less Aggregation**
4	Physically unstable	Physically unstable	**Physically stable**
5	Lipophilic as well as hydrophilic drugs are encapsulated	Lipophilic drugs are encapsulated	**Lipophilic as well as hydrophilic drugs are encapsulated**
6	More Expensive	More Expensive	**Less Expensive**
7	Batch to batch variation	Less Batch to Batch Variations	**Less Batch to Batch Variations**
8	Requirement of special precautions and conditions for formulation of preparation	Requirement of special precautions and conditions for formulation of preparation	**No requirement of special precautions and conditions for formulation of preparation**
9	Hydrolysis of encapsulated drugs	Hydrolysis of encapsulated drugs	**Less hydrolysis of encapsulated drugs**

The advancement in the niosomes leads to the evolution of proniosomal delivery systems. Proniosomes are non-ionic based surfactant vesicles, which may be hydrated immediately before use to yield aqueous niosome dispersions. Proniosomes are now a days are used to enhance drug delivery in addition to conventional niosomes.

Carrier + Surfactant = Proniosomes.

Proniosomes + water = Niosomes.

Types of Proniosomes:

1) Dry granular Proniosomes

2) Liquid crystal Proniosomes

Composition of dry granular proniosomes:

Dry granular proniosome formulation comprises of various ingredients such as drug, surfactants, carrier materials, membrane stabilizers and charge inducers.

Table : Composition of proniosome

Sr. No.	Ingredient	Example
1	Surfactants	Fatty alcohol – Oleyl alcohol, Cetostearyl alcohol, stearyl alcohol, Cetyl alcohol. Ehers – Nonoxynol-9, Octylglucoside, Lauryl glucoside, Decylglucoside, Brij,Triton X -100. Esters – Spans, Polysorbates, Glyceryllaurate. Black copolymers – Poloxamers, & etc.
2	Carrier materials	Sorbitol, Maltodextrin, Spray dried lactose, magnesium aluminium silicate, Mannitol, Sucrose stearate, microcrystalline cellulose, Glucose monohydrate, Lactose monohydrate, & etc.
3	Membrane stabilizers	Cholesterol, Lecithin, mystryl alcohol, & etc.
4	Charge inducers	Dicetyl Phosphate, stearylamine, Solulan C24, & etc.
5	Hydration medium	Phosphate buffer pH 7.4, Hot water, & etc.

Drug:

Various classes of drugs selections for proniosomes formation based upon the below mentioned assumptions;

- Least aqueous solubility drugs.
- High dosage frequency drugs.
- Low half-life.
- Suitable for Controlled drug delivery.
- Drugs with more adverse drug reactions, & etc.

Advantages of Proniosomes:

- Both the non-ionic surfactants and phospholipids in proniosomes can act as penetration enhancers and help in diffusion of the drug.
- Proniosomes have higher advantages such as additional convenience of dosing, storage, transportation, and distribution.
- They avoid the problems associated with either the aqueous noisome dispersion, such as problems of physical stability, aggregation, fusion, and leakage.
- Proniosomes also avoid problems associated with liposomes like degradation by hydrolysis or oxidation as well as sedimentation, aggregation or fusion during storage.
- Proniosomes not only offer a promising means of drug delivery, but also could enhance the recovery rate of the skin barrier.

3. Review of Literature and Development in the subject (Previous work done in the relevant area):

- **Pinal Patel, Dr. Khushbu S. Patel (2023)**

In this study, the dry free flowing Proniosomal formulae overcome the physicochemical issue connected with niosomes might have been perfectly prepared for oral route. That Proniosomal powder might have been smoothly transferred into tablets as most favourable dosage form. The proniosomes derived suspension exhibited and effective entrapment efficiency from the homogenous nano-sized vesicle. Thus, the developed proniosomal tablet formulation may help to improve the dissolution rate and may enhance the bioavailability of clozapine.

- **B Manasa., *et* al., (2022)**

Researcher prepared and evaluate Proniosomal gel for topical drug delivery. This study prove that, the proniosomal gels are the promising approach to overcome the gastrointestinal side effects and to increase the drug bioavailability.

- **Moreshwar Patil *et* al., (2021)**

Researcher prepared proniosomal gel containing etodolac as transdermal delivery for anti inflammatory activity. The *in-vitro*, *Ex-vivo* and *in-vivo* evaluations are carried out.

- **Teaima *et* al., (2020)**

In present study, dry, free-flowing proniosome formulae which strike the physicochemical issues connected with niosomes might have been perfectly prepared for oral intake. That proniosomal powder might have been smoothly transformed into tablets as a popular dosage form. Those proniosome-derived suspension exhibited reasonable and efficient entrapment efficiency from the homogenous nano-sized vesicle. In vivo pharmacokinetic investigation indicated that TEL-loaded proniosomes processed a noteworthy change in the bioavailability compared with TEL commercial tablets. Results obtained from male albino rabbits following oral administration suggested a controlled

release profile. The proniosomes might enhance the gastrointestinal absorption, also give an acceptable and exceptionally successful procedure of delivering poorly water-soluble drugs through the advantageous oral course for administration. Consequently, the proniosome powder has the chance to be a promising carrier system in modern pharmaceutical industry.

- **Eman A. Mazyed, Sherin Zakaria (2019)**

The researcher study deals with developing clopidogrel proniosomes. Clopidogrel-based proniosomes were successfully prepared as freeflowing powders with high entrapment efficiency in the range of 83.04±1.99 to 90.14±0.30. The proniosomal formulations showed higher dissolution profile than the plain drug. Clopidogrel proniosomes prepared with cholesterol and Span 60 in a ideal ratio showed the highest in vitro release over other proniosomalformulations.Optimized was found to be free-flowing powder of good flowability that is higher than that of maltodextrin powder. The niosomal vesicles formed by hydration of optimized proniosomes were spherical in shape with better mean vesicle size and zeta potential. FTIR study confirmed the absence of any chemical interactions between clopidogrel and other excipients. DTA study showed a change of clopidogrel structure from crystalline to an amorphous state. In vivo test showed that clopidogrel proniosomal formula enhanced the antiplatelet activity of clopidogrel. This approach could be promising in enhancing the dissolution, bioavailability, and efficacy of clopidogrel as well as to decrease its adverse effects.

- **S. Gaikwad *et* al.,(2018)**

The study suggests that niosomes formulation can provide consistent and prolonged release of lovastatin from different niosomal formulations. It will lead to sustained action of the entrapped drug that reduce the side effects associated with frequent administration of the drug and potentiate the therapeutic effects of the drug. This may also provide the high absorption inside the lumen and the same may be expected even in blood circulation. The dry granular proniosomes which has been anticipated to provide

improved stability as compared to conventional vesicular delivery systems in terms of aggregation, leakage etc. For the better efficacy of the formulation refrigeration of the product is necessary. The future scopes for the work are the microbial as well as in vivo studies.There are different variables which affects on formation of proniosomes that are cholesterol,span 60 which affects on encapsulation efficiency of drug in vesicles so batch PNG4 is gives good results.

- **Tamer M. Shehata *et* al., (2014)**

In this study, researcher prepared proniosomes as free-flowing solid powders, which can be further processed into tablets easily. Both proniosomal powder and tablet formulations showed enhanced pharmacokinetic properties of AC drug when compared to plain AC tablets. Tablet formulations of proniosomes showed a greater AUC, t1/2, Tmax, and relative bioavailability that could be promising in enhancing the anti-inflammatory effects of AC and using AC at a reduced dose regimen.

4. Objectives of Research/ Proposed Hypothesis:

Aim: Formulation development and Evaluation of Proniosomal Drug Delivery System.

Objectives of the Research Work:

- To perform Preformulation studies of selected API.
- To formulate and optimize Proniosomal formulation.
- To improve the bioavailability, drug loading capacity and biocompatibility of anticancer drug by formulating in Proniosomes.
- To release the medication in a controlled manner to obtain a continuous delivery.
- To minimize the toxicity and increase the stability of anticancer drug by encapsulating in Proniosomal system.
- To evaluate *in-vivo* bioavailability of Proniosomal formulation in comparison with pure drug in experimental animal.
- To study anticancer activity of the Proniosomal formulation.
- To perform stability study of Proniosomal formulation as per ICH guidelines.

5. Materials and Methodology to be adopted:

- **Literature review**
- **Selection and Collection of anticancer drug (Breast Cancer OR Brain Cancer OR Skin Cancer OR Cervical Cancer Targeted OR etc.) & excipients**

- **Experimental work**

A. Characterization of drug and excipients

- Spectroscopic studies
- Solubility studies
- Crystallinity studies

B. Compatibity studies

- **Formulation development**

- **Preparation of Proniosomes**

Step I: Preparation of Proniosomes

Proniosomes will be prepared by slurry method or coacervation phase seperation method or any other suitable method.

- **Evaluations:**
- **Characterization of Proniosomes**

- Angle of repose measurement
- Bulk & Tapped densities
- Hausner ratio
- Carr's Index
- Yield and drug content
- Particle size and zeta potential
- Entrapment efficiency
- Surface morphology by Transmission electron microscopy (TEM)
- Fourier transform infrared spectroscopy
- PXRD study

- Differential scanning colorimetry
- In vitro drug release from Proniosomal vesicles.

Step II: Preparation of Proniosomal formulation (Tablet/Gel).

- **Evaluations of Proniosomal Formulation (Tablet / Gel)**

Sr. No.	Evaluations of Proniosomal tablets	Evaluations of Proniosomal Gel
1	Weight variation	pH
2	Thickness	Transparency
3	Friability	Viscosity
4	Hardness	% Drug Entrapment
5	Drug content uniformity	Scanning Electron Microscopy
6	Disintegration time	In vitro diffusion study
7	Dissolution studies	Drug content
8	In vivo pharmacokinetic study for best formulation in animal model	Anticancer Activity by animal model
9	Anticancer Activity by animal model	Stability studies as per ICH guidelines
10	Stability studies as per ICH guidelines	

6. Importance of study/ Society application:

- **International status:** Nanotechnology is a rapidly evolving domain, as it answers to various issues associated with conventional drug delivery.This is very true in diseases like cancer where there are many challenges. Worldwide there is increasing number of cancer patients, consequently anticancer drug use also increased. Most of the studies in last few years with nanoparticulates showed a promising result and accordingly there is increasing number of patents on novel drug delivery in chemotherapy of cancer.
- **National status:** Being a second largest populated country in the world, India is facing a many more challenges in cancer therapy. Increased number of cancer patients in India due to smoking, sedentary life style, poor living standard, pollution, lack of awareness on cancers early signs and symptoms etc. A big issue in India is lack of availability of most effective, safe and economic drug delivery for cancer chemotherapy. Proniosomes have the potential to overcome the challenges related to cancer chemotherapy. There is huge scope in India to develop a drug delivery with improved efficacy, biocompatibility, biodistribution and minimized toxicity incancer chemotherapy.

►Significance of the study:

At present anticancer drug therapy has many challenges like drug resistance, lack of selectivity, lack of drug solubility, dynamic changes of cancer cells, serious side effects of chemotherapy, poor targeting of heterogenic tumors, small amount of drug reaches the cancer cell, inability of the drug to enter the core of the tumors, resulting in impaired treatment with reduced dose and survival rate etc. In reference to these challenges, it becomes necessary to formulate a novel drug delivery system which is promising, more effective and safe.

The Proniosomalformulationbears potential for the development of innovative pharmaceuticals due to its many advantages such as biocompatibility, increased drug entrapment capacity, ease and safety of production, reduced side effects and improved efficacy.In recent studies Proniosomal delivery with anticancer drug showed improved bioavailability, biocompatibility, efficacy, drug loading capacity and decreased toxicity. Hence it is need of hour to develop a formulation of the anticancer drugs in Proniosomal system.

7. Proposed work Plan/ Formulation and Structure of Study:

Year-wise Plan of work and targets to be achieved:

Sr. No.	Expected target to be achieved	1-6 months	7-10 months	11-22 months	22--27 months	28- 33 months	34-36 Month
01	Literature survey	Literature survey					
02	Selection and collection of drug and excipients	Selection and collection of drug and excipients					
03	Formulation development and optimization	Formulation development and optimization					
04	Evaluation of Proniosomal formulation	Evaluation of Proniosomal formulation					
05	*In vitro* and *in vivo* study	In vitro and in vivo study					
06	Statistical Analysis, Data Interpretation and Conclusions	Statistical Analysis, Data Interpretation and Conclusions					
07	Publishing Research and submitting data	Publishing Research and submitting data					

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